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(19)

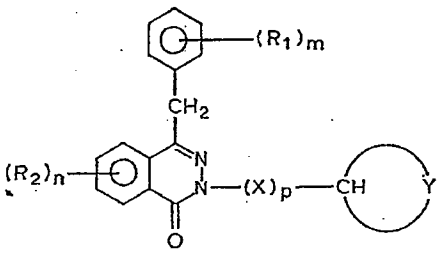
(54) BASICALLY SUBSTITUTED BENZYL-PHTHALAZINONE DERIVATIVES, ACID ADDITION SALTS THEREOF AND PROCESS FOR THE PRODUCTION THEREOF

(71) We, ASTA-WERKE AKTIENGESELLSCHAFT CHEMISCHE FABRIK, a company organised under the laws of Germany of, 4812 Brackwede, Westfalen, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

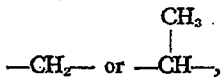
The present invention is related to new basically substituted benzyl-phthalazinone derivatives having a high antihistamine effectiveness, the physiologically acceptable acid addition salts thereof, and a process for the production thereof.

The new benzyl-phthalazinone derivatives according to the present invention are characterized by a cyclic basic residue which is connected to the nitrogen atom in the position 2 of the phthalazinone nucleus by a carbon atom of this cyclic basic residue directly or by way of an alkylene chain. Basically substituted phthalazinones are known already, for instance from German patent specification No. 1,046,625. These phthalazinones are compounds having a basic residue substituted on an alkylene chain, this basic residue being derived from a tertiary amine having two alkyl groups or an alkylene group (thus forming a cyclic residue). However, the cyclic basic residue is connected to the nitrogen atom in the position 2 of the phthalazinone nucleus by the nitrogen atom of the amine by way of the alkylene chain.

Accordingly the present invention provides a basically substituted benzyl-phthalazinone derivative of formula I



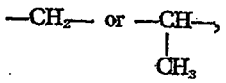
wherein R_1 and R_2, which may be identical or different from each other, represent a hydrogen or halogen atom, an alkyl radical containing from 1 to 4 carbon atoms, an alkoxy radical containing from 1 to 4 carbon atoms, or a hydroxy, trifluoromethyl, nitro or substituted or unsubstituted amino group, X is an alkylene group having the formula



m and n, which may be identical or different from each other, represent 1, 2 or 3, p is 0 or 1, and the group

is an N—C_{1-4} - alkyl - substituted pyrrolidinyl, an N—C_{1-4} alkyl - sub-

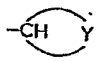
stituted piperidyl, an N—C_{1-4} - alkyl-substituted perhydroazepinyl, quinuclidinyl, tropanyl or scopyl group, the tropanyl or scopyl group being connected to the 2-nitrogen atom of the phthalazinone directly by way of a ring carbon atom of this tropanyl or scopyl group, and the other groups being connected to the 2-nitrogen atom of the phthalazinone directly or by way of an alkylene group of the formula



and their physiologically acceptable acid addition salts.

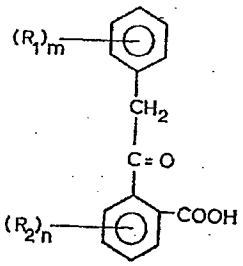
In view of their particularly good properties those compounds of formula I and their physiologically acceptable acid addition salts are preferred wherein R_1 and R_2 represent hydrogen, halogen, hydroxy, an alkyl group containing from 1 to 4 carbon atoms, an alkoxy group containing from 1 to 4 carbon atoms or trifluoromethyl, and m and n are 1 or 2. Particularly preferred are those compounds of this preferred group wherein R_1 represents such an atom or group as indicated above and R_2 is a hydrogen atom.

The most preferred group of compounds of formula I and their physiologically acceptable acid addition salts comprises those compounds wherein R_1 is a hydrogen, fluorine, chlorine or bromine atom or a methoxy, ethoxy, methyl, hydroxy or trifluoromethyl group, R_2 is a hydrogen atom, m is 1 or 2, p is 0, and the group



is the N-methyl-perhydroazepinyl, the tropanyl or the quinuclidinyl group, in particular the N-methyl-perhydroazepinyl-(4), the tropanyl-(3) or the quinuclidinyl (3) group. Thus, the fused benzene ring of these benzyl-phthalazinone derivatives is unsubstituted and the perhydroazepinyl, tropanyl or quinuclidinyl residue is connected directly to the 2-nitrogen atom of the phthalazinone nucleus.

The process for producing the new, basically substituted benzyl-phthalazinone derivatives of formula I and the physiologically acceptable acid addition salts thereof is characterized in that A) a compound of formula II

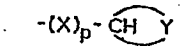


II

or a reactive derivative thereof, wherein R_1, R_2, m and n have the same meanings as in formula I, is subjected to reaction with a hydrazine of formula III

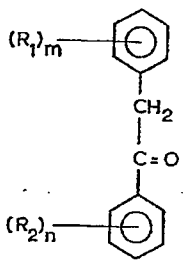
III

wherein R_3 is hydrogen or the group



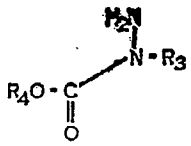
wherein X, p and —CHY have the same meanings as in formula I, or

B) a compound of formula IV



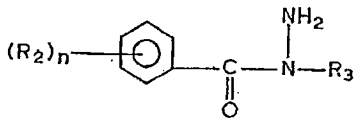
IV

wherein R_1, R_2, m and n have the same meanings as in formula I, is subjected to reaction with a compound of formula V



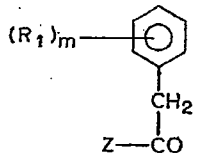
V

wherein R_3 has the same meaning as in formula III and R_4 is an alkyl group containing from 1 to 4 carbon atoms, or



VI

wherein R_2 and n have the same meanings as in formula I and R_3 has the same meaning as in formula III, is subjected to reaction with a compound of formula VII



VII

wherein R_1 and m have the same meanings as in formula I and Z is a halogen atom or a hydroxy or alkoxy group, or

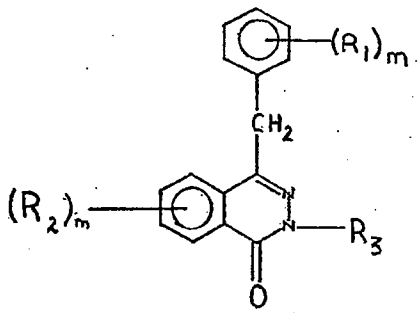
D) when

is an

N—C_{1-4} alkyl-substituted pyrrolidinyl,
N—C_{1-4} alkyl-substituted piperidyl
or N—C_{1-4} alkyl-substituted perhydroazepinyl group,

a compound of formula I wherein the group

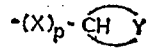
is a pyrrolidinyl group, a piperidyl group or a perhydroazepinyl group is subjected to reaction with an alkylating agent containing from 1 to 4 carbon atoms and subjecting a benzyl-phthalazinone derivative of formula XIII



wherein R_1, R_2, m and n have the same meaning as in formula I and R_3 is hydrogen, resulting from process A), B), or C), to reaction with a compound of formula VIII

$$Q—R_3$$

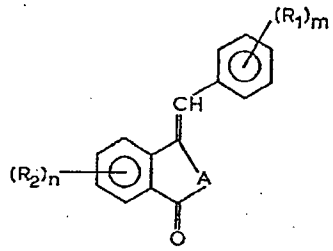
wherein Q represents an atom or group which, upon substitution of the amide group, is split off together with its electron doublet, such as a halogen atom or a sulphonic ester group, and R_3 is the group



X, p and

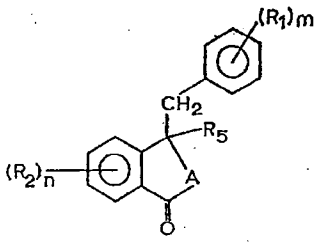
having the same meanings as in formula I, and converting the thus obtained benzyl-phthalazinone derivative, if desired, with an appropriate acid into a physiologically acceptable acid addition salt thereof or if desired, converting a resulting salt of a benzyl-phthalazinone derivative into the free base.

A reactive derivative of the carboxylic acid of formula II is in particular an acid halide, ester or anhydride. Other reactive derivatives of the compounds of formula II which may be used are the unsaturated or saturated phthalides or phthalimidines of the formula X



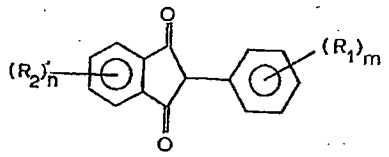
X

and XI



XI

In the above formulas X and XI, R_1, R_2, m and n have the same meanings as in formula I and A is an oxygen atom or imino group and R_3 is halogen, NH_2, ArNH (wherein Ar represent an aryl group), OH or an alkoxy group. Other compounds of this type are those of formula XII



XII

wherein R_1, R_2, m and n have the same meanings as in formula I. These compounds produce derivatives of the compound of formula II when subjected to reaction with a compound of formula III.

The above procedures A, B and C are carried out in the absence or presence of usual solvents and auxiliary agents at a temperature elevated up to about 180° C. and in a pH range varying from acidic to alkaline.

Useful solvents are, for instance, water, alcohols, dimethyl-formamide, dioxane, pyridine, triethylamine and hydrocarbons. Useful auxiliary agents are bases, acids and condensation agents usual for such reactions.

The procedure D is carried out with usual alkylating agents such as formaldehyde in the presence of a reducing agent such as formic acid, $NaBH_4$ or hydrogen, as well as dimethyl sulfate and K_2CO_3, alkyl halides or diazomethane. The reaction E preferably is carried out with catalytic hydrogen. Useful catalysts are preferably the precious metal and nickel catalysts.

When carrying out the reaction with the alkylating agents of formula VIII, the known cyclammonium rearrangements [See Henecka, Hörlein und Risse "Zur Kenntnis dercycloammonium-Umlagerung" Ang. Chem. *72*, 960(1960] may take place with a change in the ring size.

The compounds of formula I and their acid addition salts are to a great extent optically active by way of the carbon atom of the cyclic basic group which is connected to the amide nitrogen atom of the phthalazinone nucleus directly or by way of an alkylene group. The racemates may be split up into the optically active antipodes in a manner known *per se*.

The compounds according to the present invention are histaminolytically active. They are characterized by an extremely high activity upon parenteral and above all oral application. They furthermore produce this high activity over a long period of time. This activity may be shown in the histamine aerosol test on guinea-pigs or in the lesion test in humans, the lesion being caused by histamine or a histamine liberator (Quaddel-Test).

In guinea-pigs, the histaminolytical activity has been tested in the histamine aerosol test. Guinea-pigs of the Pirbright race weighing 300 to 700 grams each have been tested. The animals inhale an aerosol of an aqueous solution of histamine dihydrochloride in a concentration of 4 mg./ml. The inhalation produces severe dyspnea (severe shortness of breath, lateral positioning) in untreated animals within 2 minutes. In order to determine the histaminolytical activity, the test compounds are applied subcutaneously or orally to groups of 8 to 10 animals. Thereafter, the test animals are treated for varying times with the histamine aerosol. The test animals are considered as protected if they tolerate the inhalation of the aerosol for 10 minutes without showing severe dyspnea (lateral positioning).

For evaluating the test results, the mean effective doses (ED 50 mg./kg.) are determined by means of a probit analysis from the relation between the dose logarithm and the frequency of protection.

Compounds which are similar in chemical structure to the compounds of the present invention and, therefore, have been used for comparative tests, are 4-benzyl-2-(2-dimethylaminoethyl) - 1 - (2H) - phthalazinone ("Ahanon" according to German patent specification No. 1,046,625; compound A in Tables I and II) and β-dimethylaminoethyl-(4-chloro-α-methyl-benzhydryl)-ether, known as a highly active histaminolytic (generic name: chlorophenoxamine; H. Arnold et al., Arzneim-Forsch. *4*, 189 (1954); N. Brock et al., Arzneim.-Forsch. *4*, 262 (1954); compound B in Tables I and II).

The difference between the products according to the present invention and the comparative products A and B is particularly obvious when administering the test compounds to the test animals orally and treating the test animals with the histamine aerosol 8 hours later. Upon application of 0.0215 mg./kg. of 4 - (*p* - fluorobenzyl) - 2 - [N - methyl-perhydroazepinyl - (4)] - 1 (2H) - phthalazinone or 0.215 mg./kg. of 4-(*p*-chlorobenzyl) - 2 - [N - methyl - perhydroazepinyl-(4)] - 1 - (2H) - phthalazinone or 4 - (*p*-chlorobenzyl) - 2 - [quinuclidinyl - (3)] - 1-(2H)-phthalazinone, not one of the 8 to 10 animals of each group showed dyspnea with lateral positioning after treatment with the histamine aerosol. In striking contrast thereto, upon application of 10 to 100 times the dose of both comparative compounds (2.15 mg./kg.) 9 of 10 animals with compound A and 10 of 10 animals with compound B still showed very severe dyspnea with lateral positioning.

TABLE I

Histaminolytical activity in the histamine aerosol test on guinea-pigs; subcutaneous administration of test compounds 1 hour before treatment with the aerosol

Example No.	ED 50 [mg./kg.]	relative activity (activity of A=1.00)
3	0.0062	17.7
6	0.011	10.0
7	0.0071	15.5
9	0.045	2.44
10	0.031	3.55
11	0.035	3.14
12	0.022	5.00
19	0.016	6.88
24	0.027	4.07
28	0.059	1.86
30	0.026	4.23
33	0.016	6.88
34	0.119	5.79
A	0.11	1.00
B	0.11	1.00

TABLE II

Histaminolytical activity in the histamine aerosol test on guinea-pigs; oral administration of test compounds 2 and 8 hours before treatment with the aerosol.

Example No.	ED 50 [mg./kg.]		relative activity (activity of A=1.00)	
	2 hours	8 hours	2 hours	8 hours
9	0.16	0.49	19.4	13.1
10	0.037	0.029	83.8	221
19	0.010	0.011	310	582
24	0.087	0.052	35.6	123
28	0.20	0.28	15.5	22.9
30	0.038	0.35	81.6	18.3
A	3.1	6.4	1.00	1.00
B	0.52	6.2	5.96	1.03

The histaminolytical activity of the compounds according to the present invention is substantially higher than those of the comparative test compounds A and B. Upon subcutaneous administration, the relative activity is about 17.7 times larger (Example No. 3) than that of the comparative test compounds. The activity is particularly evident upon oral administration (Table II). The activity is 16 to 310 times higher in a 2 hours test in comparison to the activity of test compound A and is 13 to 582 times higher in the 8 hours test. The 8 hours test clearly demonstrates the very high oral activity of the compounds according to the present process which activity is produced over a prolonged period of time.

The compounds according to the present invention are used as active ingredients in pharmaceutical preparations and may be administered in usual embodiments such as tablets, dragees, capsules, suppositories, drops, ointments, creams and injection solutions. They are in particular used for the treatment of the various forms of allergies. Thus, they have been used successfully in humans in the treatment of bronchial asthma, for the treatment of disorders of the skin and mucous membranes such as urticaria, Quincke's edema, pruritus, eczemas, hay fever and rhinitis vasomotorica. In general, they are administered in such treatments in a dosage of 0.4 to 4 mg. per day. The symptoms of the above allergic diseases may be effectively reduced upon a single dose for up to 24 hours. The effectiveness of the compounds of the present invention in humans, which is produced very rapidly and over a prolonged period of time in comparison to other antihistamines, may be particularly well shown in the reduction of the size of an artificially produced lesion by means of a histamine liberator according to L. Kerp, H. Kasimir, P. N. Tie, Med. Welt 17 NF, 2794 (1966). The compounds according to the present invention may be used as such or in combination with other active ingredients as is usual in antihistaminic preparations. In this respect their minimal dose is most advantageous.

The present invention is further illustrated by the following examples. The constitution of the final products has been verified by elementary analysis and infrared and NMR spectra.

Example 1.

4-Benzyl-2-[N-methylpyrrolidinyl-(3)-methyl]-1-(2H)-phthalazinone.

10.3 g. of α-phenylacetophenone-*o*-carboxylic acid and 6.1 g. of hydrazine sulfate are dissolved in a solution of 3.6 g. of NaOH in 100 cc. of water. The solution is heated to boiling for 2 hours. The precipitate is filtered off with suction, washed with water and dried. The thus obtained 9.2 g. of 4-benzyl-1-(2H)-phthalazinone are added to a solution of 1.4 g. of metallic potassium in 250 cc. of anhydrous alcohol. The resulting mixture is heated to boiling for 30 minutes. The alcohol is distilled off. 10.6 g. of the potassium salt are obtained.

12.4 g. of the tosyl ester of 3-hydroxymethyl-N-methylpyrrolidine and 10.6 g. of

the potassium salt of 4-benzyl-1 (2H)-phthalazinone in 100 cc. of dimethylformamide are heated for one hour at 100° C. The solvent is separated in a rotary evaporator and the residue is triturated with water. The insoluble matter is dissolved in ether and the ethereal solution is extracted with dilute hydrochloric acid. The acidic extracts are rendered alkaline by the addition of an aqueous potassium hydroxide solution. The separated oily product is dissolved in ether and the ethereal solutions are dried over anhydrous Na_2SO_4. Upon evaporation of the ether, 11 g. of the base are obtained. The fumarate crystallizes as the monohydrate. M.p.: 129—132° C.

The following compounds have been prepared in a manner which is similar to the procedure of Example 1.

2. 4 - (p - Chlorobenzyl) - 2 - [N - methylpyrrolidinyl - (2) - methyl] - 1 (2H) - phthalazinone hydrochloride.
M.p.: 206—207° C.

3. 4 - (p - Chlorobenzyl) - 2 - [N - methylpiperidyl - (2) - methyl] - 1 (2H) - phthalazinone sulfate hydrate.
M.p.: above 90° C.
(with decomposition).

4. 4 - Benzyl - 2 - [N - methylpiperidyl-(3) - methyl] - 1 (2H) - phthalazinone hydrochloride hydrate.
M.p.: above 77° C.
(with decomposition).

5. 4 - (p - Methylbenzyl) - 2 - [N - methylpyrrolidinyl - (2) - methyl] - 1 - (2H)-phthalazinone hydrochloride hydrate.
M.p.: 126—128° C.

6. 4 - (p - Methoxybenzyl) - 2 - [N-methylpyrrolidinyl - (2) - methyl] - 1 - (2H)-phthalazinone.
M.p.: 111—114° C.

7. 4 - (p - Chlorobenzyl) - 2{1 - [N-methyl - piperidyl - (2)] - ethyl} - 1 - (2H)-phthalazinone citrate.
M.p.: 103—105° C.

Example 8.

4 - Benzyl - 2 - [N - methyl - perhydroazepinyl - (4)] - 1 - (2H) - phthalazinone.

A solution of 8 g. of 4-chloro-N-methylperhydroazepine in 20 cc. of toluene is added to a suspension of 13.7 g. of the potassium salt of 4-benzyl-1-(2H)-phthalazinone in 250 cc. of anhydrous toluene dropwise with rapid stirring at 40° C. Heating is applied slowly up to boiling whereafter refluxing is continued for another 5 hours. The solvent is separated in a rotary evaporator and the residue is washed with water. The insoluble oily product is dissolved in ether and the ethereal solution is extracted with dilute hydrochloric acid. The acidic extracts are rendered alkaline by the addition of aqueous potassium hydroxide and the separated oil is again dissolved in ether. The ethereal solutions are dried over anhydrous Na_2SO_4. Upon evaporation of the solvent, 32 g. of a raw product are obtained. This product is converted into the fumarate which is recrystallized, thus resulting in the fumarate hydrate of the 4 - benzyl - 2 - [N - methyl - perhydroazepinyl-(4)]-1 (2H)-phthalazinone.
M.p.: 156—160° C.

Example 9.

4-(p-Chlorobenzyl)-1-[N-methyl-perhydroazepinyl-(4)]-1 (2H)-phthalazinone.

30.6 g. of α - (p - chlorophenyl)acetophenone-o-carboxylic acid and 16 g. of hydrazine sulfate are heated with 9.4 g. of NaOH in 250 cc. of water. After washing and drying, 27 g. of 4-(p-chlorobenzyl)-1 (2H)-phthalazinone are obtained.

20 g. of 2-(2-chloroethyl)-N-methylpyrrolidine hydrochloride are added to a solution of 4.4 g. of NaOH in 20 cc. of water. This solution is heated to 70° C. and added dropwise to a mixture of the above obtained 27 g. of 4-(p-chlorobenzyl)-1 (2H)-phthalazinone and 40 cc. of 50% soda lye heated to 70° C. The mixture is kept at this temperature and heated for another hour. After cooling and diluting with water, the insoluble materials are separated and dissolved in methylene chloride. The solution is extracted with dilute hydrochloric acid and the acidic extracts are rendered alkaline by the addition of aqueous potassium hydroxide. The separated oil is again dissolved in methylene chloride and the solution is dried and evaporated. The crude final product is obtained in a yield above 90% of the theoretical. It is converted into a salt and purified by recrystallization. The hydrochloride of 4-(p-chlorobenzyl)-2-[N-methyl-perhydroazepinyl-(4)]-1 (2H)-phthalazinone melts at 225—229° C.

The following compounds have been prepared in a manner which is similar to the procedure of Examples 8 and 9.

10. 4 - (p - Methylbenzyl) - 2 - [N-methyl - perhydroazepinyl - (4)] - 1 (2H)-phthalazinone sulfate.
M.p.: 199—203° C.

11. 4 - (p - Methoxybenzyl) - 2 - [N-methyl - perhydroazepinyl - (4)] - 1 - (2H)-phthalazinone sulfate.
M.p.: 203—205° C.

12. 4 - (3,4 - Dimethoxybenzyl) - 2 - [N-methyl - perhydroazepinyl - (4)] - 1 - (2H)-phthalazinone sulfate.
M.p.: 118—120° C.

13. 4 - (2 - Chlorobenzyl) - 2 - [N-methyl - perhydroazepinyl - (4) - 1 (2H)-phthalazinone hydrochloride.
F.p.: 198—200° C.

14. 4 - (3 - Chlorobenzyl) - 2 - [N - methyl-perhydroazepinyl - (4)] - (2H) - phthalazinone.
F.p.: 77—78° C.

15. 4 - (p - Chlorobenzyl) - 6,7 - dimethoxy - 2 - [N - methyl - perhydro-

azepinyl - (4)] - 1 (2H) - phthalazinone sulfate.
F.p.: 286—290° C.
16. 4 - (2,4 - Dichlorobenzyl) - 2 - [N-methyl - perhydroazepinyl - (4)] - 1 - (2H)-phthalazinone fumarate.
F.p.: 207—211° C.
17. 4 - (p - Dimethylaminobenzyl) - 2-[N - methyl - perhydroazepinyl - (4)] - 1 (2H) - phthalazinone fumarate.
F.p.: 177—182° C.
18. 4 - (p - Fluorobenzyl) - 2 - [N-methyl - perhydroazepinyl - (4)] - 1 (2H)-phthalazinone sulfate.
F.p.: 211—220° C.
19. 4 - (p - Bromobenzyl) - 2 - [N-methyl-perhydroazepinyl - (4)] - 1 (2H) - phthalazinone sulfate.
F.p.: 215—220° C.
20. 4 - (p - Acetylaminobenzyl) - 2 -[N-methyl - perhydroazepinyl - (4)] - 1 (2H)-phthalazinone hydrochloride hydrate.
F.p.: 275—278° C.
21. 4 - (p - Aminobenzyl) - 2 - [N-methyl - perhydroazepinyl - (4)] - 1 (2H)-phthalazinone dihydrochloride hydrate.
F.p.: 270—277° C.
22. 4 - (p - Hydroxybenzyl) - 2 - [N-methyl - perhydroazepinyl - (4)] - 1 (2H)-phthalazinone hydrochloride hydrate.
F.p.: 260—266° C.

Example 23.

4 - (p - Chlorobenzyl) - 2 - [quinuclidinyl-(3)] - 1 (2H) - phthalazinone.

5.5 g. of α - (*p* - chlorophenyl) acetophenone-*o*-carboxylic acid are dissolved in 30 cc. of 2N soda lye and 30 cc. of water. 4.3 g. of 3-quinuclidinyl-hydrazine dihydrochloride are added thereto and the mixture is heated to boiling for 3 hours under an atmosphere of nitrogen. Upon cooling, a highly viscous red oil is separated which crystallizes upon scratching. The solid material is filtered off, washed with water and recrystallized. 4.4 g. of 4-(*p*-chlorobenzyl)-2-[quinuclidinyl-(3)]-1 (2H)-phthalazinone are obtained. This product melts at 181—182° C.

Example 24.

4-(p-Chlorobenzyl)-2-[N-methylpiperidyl-(4)]-1 (2H)-phthalazinone.

11 g. of α-(*p*-chlorophenyl)acetophenone-*o*-carboxylic acid are dissolved in 120 cc. of ethyl alcohol. A solution of 8 g. of N-methylpiperidyl-(4)-hydrazine dihydrochloride is added thereto and the mixture is heated to boiling for 8 hours under an atmosphere of nitrogen. The alcohol is distilled off and the residue is triturated with dilute soda lye. The insoluble oily product is dissolved in chloroform and the chloroform solution is washed and dried. Upon evaporation, 8.4 g. of the phthalazinone base are obtained. The fumarate melts at 191—193° C.

The following compounds have been prepared in a manner which is similar to the procedure of Examples 23 and 24.

25. 4 - Benzyl - 2 - [N - methylpiperidyl-(4)]-1 (2H)-phthalazinone hydrate.
M.p.: 106—110° C.
26. 4 - (p - Chlorobenzyl) - 2 - [tropanyl-(3)] - 1 (2H) - phthalazinone hydrochloride hydrate.
M.p.: 270—274° C.
27. 4 - Benzyl - 2 - [quinuclidinyl - (3)]-1 (2H)-phthalazinone fumarate hydrate.
M.p.: 233—235° C.
28. 4 - (p - Chlorobenzyl) - 2 - [N-methylpyrrolidinyl - (3)] - 1 (2H) - phthalazinone.
M.p.: 117—120° C.
29. 4 - (p - Methoxybenzyl) - 2 - [quinuclidinyl - (3)] - 1 (2H) - phthalazinone hydrochloride.
M.p.: 236—237° C.
30. 4 - (p - Fluorobenzyl) - 2 - [N-methylpyrrolidinyl - (3)] - 1 (2H) - phthalazinone.
M.p.: 90—93° C.
31. 4 - (p - Methylbenzyl) - 2 - [N-methylpyrrolidinyl - (3)] - 1 (2H) - phthalazinone.
M.p.: 96—98° C.
32. 4 - (p - Chlorobenzyl) - 2 - [perhydroazepinyl - (4)] - 1 (2H) - phthalazinone fumarate.
M.p.: decomposition.

Example 33.

4 - (p - Chlorobenzyl) - 2 - [N-methyl - perhydroazepinyl - (4)] - 1 (2H)-phthalazinone.

1.0 g. of 4-(*p*-chlorobenzyl)-2-[perhydroazepinyl-(4)]-1 (2H)-phthalazinone are heated to boiling for 5 hours with 10 g. of a 40% aqueous formaldehyde solution and 11.6 g. of formic acid. The solution is evaporated and the residue is triturated with dilute soda lye. The insoluble material is dissolved in chloroform and the chloroform solution is dried and evaporated. The residue is dissolved in ether. 0.8 g. of the hydrochloride is precipitated by the addition of ethereal hydrochloric acid. After recrystallization from alcohol, the compound melts at 225—229° C.

This compound is identical to the final product obtained according to Example 9.

The following compound has been prepared in a manner which is similar to the procedure of Example 33.

34. 2 - [N - Methyl - perhydroazepinyl-(4)] - 4 - (p - trifluoromethylbenzyl) - 1 (2H)-phthalazinone.

Example 35.

4 - (p - Chlorobenzyl) - 2 - [N - methyl-piperidyl - (3)] - 1 (2H) - phthalazinone.

4.9 g. of 3 - [4 - (*p* - chlorobenzyl)1 - oxo-phthalazinyl-(2)]-1-methyl-pyridinium iodide are subjected to hydrogenation in 300 cc. of ethyl alcohol in the presence of PtO_2 as catalyst for 7 hours at 80° C. and at a hydrogen

pressure of 100 atmospheres. The catalyst is filtered off and the alcohol is distilled off. The residue is treated with dilute soda lye and the insoluble materials are dissolved in methylene chloride. The methylene chloride solution is washed with water and dried over potash. The solvent is filtered off and the solid residue is recrystallized from 60 to 70% ethyl alcohol. The yield is 2.5 g.

M.p.: 154—156° C.

The following compounds have been prepared as described in Example 35:

36. 4 - (p - Methylbenzyl) - 2 - [N-methylpiperidyl - (3)] - 1 (2H) - phthalazinone.

M.p.: 137—139° C.

37. 4 - (p - Methoxybenzyl) - 2 - [N-methylpiperidyl - (3)] - 1 (2H) - phthalazinone.

M.p.: 87—93° C.

Example 38.

Tablets containing the products according to the present invention are prepared according to the following recipe as exemplified by the compound of Example 18:

Active ingredient according to Example 19	1.0 mg.
corn starch	51.0 mg.
secondary calcium phosphate, anhydrous	20.0 mg.
lactose	20.0 mg.
polyvinylpyrrolidone	3.0 mg.
talcum	4.0 mg.
magnesium stearate	1.0 mg.
	100.0 mg.

The active compound is dissolved together with the polyvinyl-pyrrolidone in 5 times the amount of chloroform. A homogeneous mixture of calcium phosphate, lactose and 60% of the corn starch are mixed therewith and granulated. The dried granulate sieved to a maximal particle size of 0.75 mm. is mixed with the remaining amount of corn starch, talcum and magnesium stearate for half an hour and the mixture is pressed to tablets weighing 100 mg. each and having a diameter of 6 mm.

Example 39.

As described in Example 38, dragee-kernels weighing 100 mg., having a diameter of 6 mm. and a camber diameter of 5 mm., are prepared. These kernels are coated with a usual dragee coating in an amount of 170 mg.

Another batch of kernels is sprayed with a lacquer solution instead of the dragee coating. The resulting lacquer coating comprises:

Hydroxypropylmethyl cellulose	1.6 mg.
ethyl cellulose	0.5 mg.
polyethyleneglycol 4000	0.4 mg.
1,2-propylene glycol	0.25 mg.
titanium dioxide	0.25 mg.

The above recipes of the Examples 28 and 29 may be further followed by using a smaller amount of the active ingredient, such as 0.6 and 0.3 mg. instead of 1 mg. The difference in weight is balanced by additional amounts of corn starch.

Example 40.

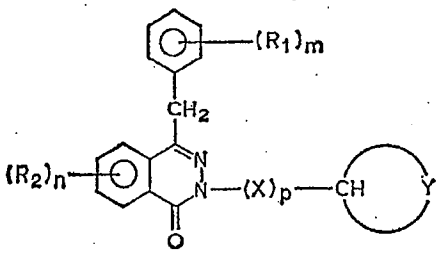
1 g. of the hydrochloride of active ingredient of Example 9 are milled to a particle size of less than 75μ. The resulting product is mixed slowly with 999 g. of molten suppository fat at 40° C. with rapid stirring. The homogeneous mixture is poured into suppository molds to give suppositories each weighing 1.0 g. In an analogous manner, suppositories may be prepared containing 0.5 mg., 2 mg. or 6 mg. of active ingredient.

Exaxmple 41.

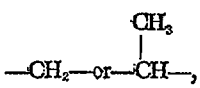
300 mg. of the hydrochloride corresponding to the product of Example 18 are dissolved together with 855 mg. of sodium chloride in 90 cc. of water and the solution is made up to 100 cc. The resulting solution is thoroughly filtered and poured into ampoules each measuring 1.1 cc. The closed ampoules are sterilized in an autoclave with steam under pressure at at least 120° C. for half an hour.

WHAT WE CLAIM IS:—

1. A basically substituted benzyl-phthalazinone derivative of formula I

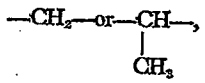


wherein R_1 and R_2, which may be identical or different from each other, represent a hydrogen or halogen atom, an alkyl radical containing from 1 to 4 carbon atoms, an alkoxy radical containing from 1 to 4 carbon atoms, or a hydroxy, trifluoromethyl, nitro or substituted or unsubstituted amino group, X is an alkylene group having the formula



m and n, which may be identical or different from each other, represent 1, 2 or 3, p is 0 or 1, and the group

is an N—C_{1-4} alkyl-substituted pyrrolidinyl, an N—C_{1-4}-alkyl-substituted piperidyl, an N—C_{1-4}-alkyl-substituted perhydroazepinyl, quinuclidinyl, tropanyl or scopyl group, the tropanyl or scopyl group being connected to the 2-nitrogen atom of the phthalazinone directly by way of a ring carbon atom of this tropanyl or scopyl group, and the other groups being connected to the 2-nitrogen atom of the phthalazinone directly or by way of an alkylene group of the formula



and their physiologically acceptable acid addition salts.

2. A basically substituted benzyl-phthalazinone derivative as claimed in claim 1 wherein R_1 and R_2 represent hydrogen, halogen, hydroxy, an alkyl group containing from 1 to 4 carbon atoms, an alkoxy group containing from 1 to 4 carbon atoms or trifluoromethyl, and m and n are 1 or 2.

3. A basically substituted benzyl-phthalazinone derivative as claimed in claim 1 or 2 wherein R_2 is hydrogen.

4. A basically substituted benzyl-phthalazinone derivative as claimed in any of claims 1 to 3 wherein R_1 is a hydrogen, fluorine, chlorine or bromine atom or a methoxy, ethoxy, methyl, hydroxy or trifluoromethyl group, R_2 is a hydrogen atom, m is 1 or 2, p is 0 and the group

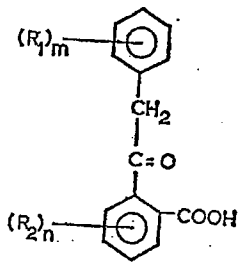
is the N-methyl-perhydroazepinyl, the tropanyl or the quinuclidinyl group.

5. A basically substituted benzyl-phthalazinone derivative as claimed in claim 4 wherein R_1 is *p*-chloro or *p*-fluoro and the group

is the N-methyl-perhydroazepinyl-(4) group.

6. A process for the production of a basically substituted benzyl-phthalazinone derivative as claimed in any of claims 1 to 5, comprising

A) subjecting a compound of Formula II



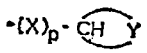
II

or a reactive derivative thereof, wherein R_1, R_2, m and n have the same meanings as in claims 1 to 5,

to reaction with a hydrazine compound of formula III

III

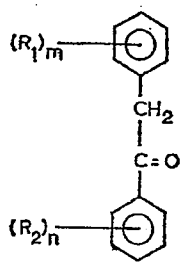
wherein R_3 is hydrogen or the group



X, p and

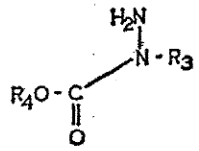
having the same meanings as in claims 1 to 5, or

B) subjecting a compound of formula IV



IV

wherein R_1, R_2, m and n have the same meanings as in claims 1 to 5 to reaction with a compound of formula V

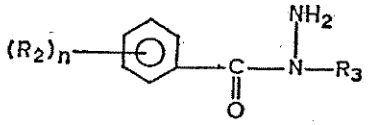


V

wherein R_3 has the same meaning as in formula III and R_4 is an alkyl group containing from 1 to 4 carbon atoms,

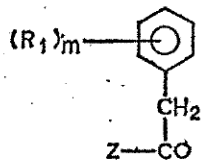
or

C) subjecting a compound of formula VI



VI

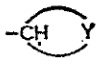
wherein R_2 and n have the same meanings as in claims 1 to 5 and R_3 has the same meaning as in formula III, to reaction with a compound of formula VII



VII

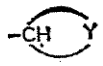
wherein R_1 and m have the same meanings as in claims 1 to 5, and Z is a halogen atom or a hydroxy or alkoxy group, or

D) when

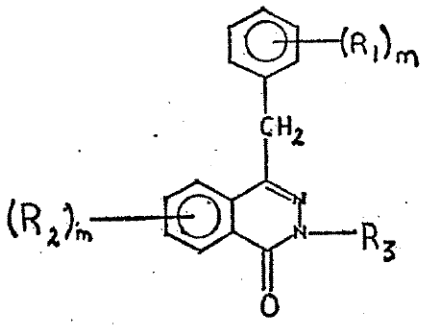


is an N—C_{1-4} alkyl-substituted pyrrolidinyl, N—C_{1-4} alkyl-substituted piperidyl or N—C_{1-4} alkyl-substituted perhydroazepinyl group,

subjecting a compound of formula I as defined in claim 1, wherein the group



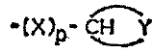
is a pyrrolidinyl group, a piperidyl group or a perhydroazepinyl group to reaction with an alkylating agent, containing 1 to 4 carbon atoms, and subjecting a benzyl-phthalazinone derivative of formula XIII



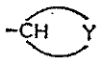
wherein R_1, R_2, m and n have the same meaning as in formula I and R_3 is hydrogen, resulting from process A), B) or C), to reaction with a compound of formula VIII

$$Q—R_3$$

wherein Q represents an atom or group which, upon substitution of the amide group, is split off together with its electron doublet and R_3 is the group



X, p and



having the same meanings as in claims 1 to 5, and converting the thus obtained benzyl-phthalazinone derivative, if desired, with an appropriate acid into a physiologically acceptable acid addition salt thereof or, if desired, converting a resulting salt of a benzyl-phthalazinone derivative into the free base.

7. A process as claimed in claim 6 wherein Q is a halogen atomor a sulphonic ester group.

8. The final product of each of the individual Examples 1—37 herein.

9. A process as claimed in claim 6 substantially as described with reference to any of Examples 1 to 37.

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(1)

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(an international survey)

6th revised and enlarged edition

by

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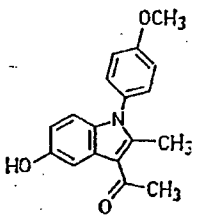
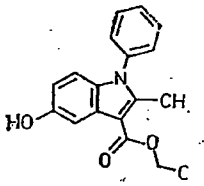


5-Hydroxy-1-(*p*-me
dolyl methyl keto
methoxyphenyl)-2-
1-(4-methoxypheny
ethanone (•)

S Amendol

U Antidepressant

4714

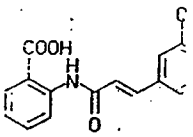


Ethyl 5-hydroxy-2
oxylate = 5-Hyd
dole-3-carboxylic a

S Oksifemedol, Ox

U Antihypertensiv

4715



N-(3,4-Dimethoxy
2-[[3-(3,4-Dimetho
amino]benzoic acid

S *N*-5', Rizaben, 7

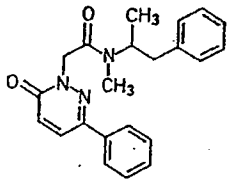
U Anti-allergic, an

MP0286

S THC, Thioban, *Thiocarbanidin*, Y 9525

U Tuberculostatic

6495 *(4839)* $C_{22}H_{23}N_3O_2$ 55902-02-8

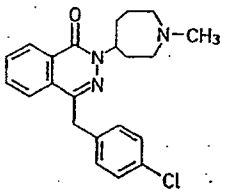


(−)-*N*-Methyl-*N*-(1-methyl-2-phenylethyl)-6-oxo-3-phenyl-1(6*H*)-pyridazineacetamide (•)

S *Isamfazone***, Pir-353

U Anti-inflammatory

6496 *(6560)* $C_{22}H_{24}ClN_3O$ 58581-89-8



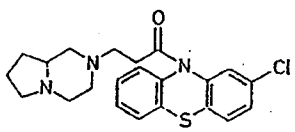
4-(*p*-Chlorobenzyl)-2-(hexahydro-1-methyl-1*H*-azepin-4-yl)-1(2*H*)-phthalazinone = 4-[(4-Chlorophenyl)methyl]-2-(hexahydro-1-methyl-1*H*-azepin-4-yl)-1(2*H*)-phthalazinone (•)

R Monohydrochloride (79307-93-0)

S A-5610, Asta A 5610, *Azelastine hydrochloride***, Azeptin

U Antihistaminic, anti-asthmatic

6497 *(4840)* $C_{22}H_{24}ClN_3OS$ 49864-70-2



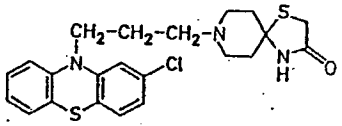
2-Chloro-10-[3-(hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)propionyl]phenothiazine = 2-Chloro-10-[3-(hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)-1-oxopropyl]-10*H*-phenothiazine (•)

R Dihydrochloride (49780-10-1)

S AY-25329, *Azaclorzine dihydrochloride***, Nonachlazin

U Coronary vasodilator

6498 *(4841)* $C_{22}H_{21}ClN_3OS_2$ 24527-27-3



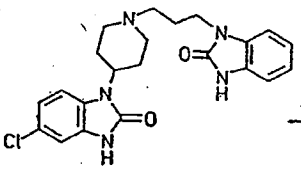
8-[3-(2-Chloro-10-phenothiazinyl)propyl]-1-thia-4,8-diazaspiro[4.5]decan-3-one = 8-[3-(2-Chloro-10*H*-phenothiazin-10-yl)propyl]-1-thia-4,8-diazaspiro[4.5]decan-3-one (•)

R Monohydrochloride (27007-85-8)

S APY-606, *Clospirazine hydrochloride*, Diceplon, Disepron, *Spiclomazine hydrochloride***

U Psychotropic

6499 *(6561)* $C_{22}H_{24}ClN_5O_2$ 57808-66-9

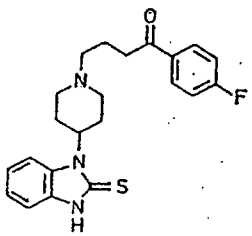


5-Chloro-1-[1-[3-(2-oxo-1-benzimidazolinyl)propyl]-4-piperidyl]-2-benzimidazolinone = 5-Chloro-1-[1-[3-(2,3-dihydro-2-oxo-1*H*-benzimidazol-1-yl)propyl]-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one (•)

S Cilroton, *Domperidone***, Ecuamon, Euciton, KD 5338, Moperidona, Motilium, Nauseline, Nauzelin, Peridal, Peridon, Pleiadon, R 33812, Sibrinal

U Anti-emetic

6500 $C_{22}H_{24}FN_3OS$ 57648-21-2



Europäisches Patentamt

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Kategorie	Kennzeichnung des Dokuments mit Angabe, soweit erforderlich, der maßgeblichen Teile	Betrifft Anspruch	KLASSIFIKATION DER ANMELDUNG (Int. Cl.4)
D,Y	DE-A-2 164 058 (ASTA-WERKE A.G.) * Seite 15, Zeile 12 - Seite 16, Zeile 10; Beispiel 46 * --	1-7,9	A 61 K 31/55 A 61 K 9/06
Y	DE-A-3 530 793 (ASTA-WERKE AG) * Seite 14, Zeile 1 - Seite 18, Zeile 9; Seite 19, Zeilen 28-30; Seite 20, Zeilen 11-29; Ansprüche 1-6 *	1-7,9	

RECHERCHIERTE SACHGEBIETE (Int. Cl.4): A 61K

UNVOLLSTÄNDIGE RECHERCHE

Nach Auffassung der Recherchenabteilung entspricht die vorliegende europäische Patentanmeldung den Vorschriften des Europäischen Patentübereinkommens so wenig, daß es nicht möglich ist, auf der Grundlage einiger Patentansprüche sinnvolle Ermittlungen über den Stand der Technik durchzuführen.

Vollständig recherchierte Patentansprüche: 1-7,9
Unvollständig recherchierte Patentansprüche: 8
Nicht recherchierte Patentansprüche:
Grund für die Beschränkung der Recherche:

Verfahren zur chirurgischen oder therapeutischen Behandlung des menschlichen oder tierischen Körpers (Siehe Art. 52(4) des Europäischen Patentübereinkommens)

Recherchenort	Abschlußdatum der Recherche	Prüfer
Den Haag	17-02-1989	TZSCHOPPE

KATEGORIE DER GENANNTEN DOKUMENTEN
X : von besonderer Bedeutung allein betrachtet
Y : von besonderer Bedeutung in Verbindung mit einer anderen Veröffentlichung derselben Kategorie
A : technologischer Hintergrund
O : nichtschriftliche Offenbarung
P : Zwischenliteratur
T : der Erfindung zugrunde liegende Theorien oder Grundsätze

E : älteres Patentdokument, das jedoch erst am oder nach dem Anmeldedatum veröffentlicht worden ist
D : in der Anmeldung angeführtes Dokument
L : aus andern Gründen angeführtes Dokument

& : Mitglied der gleichen Patentfamilie, übereinstimmendes Dokument

MP0288

ANHANG ZUM EUROPÄISCHEN RECHERCHENBERICHT ÜBER DIE EUROPÄISCHE PATENTANMELDUNG NR.

EP 88 11 7902

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten europäischen Recherchenbericht angeführten Patentdokumente angegeben.
Die Angaben über die Familienmitglieder entsprechen dem Stand der Datei des Europäischen Patentamts am 13/03/89
Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie		Datum der Veröffentlichung
DE-A- 2164058	27-07-72	NL-A-	7200400	25-07-72
		FR-A,B	2122517	01-09-72
		GB-A-	1377231	11-12-74
		AT-A,B	313288	15-01-74
		AU-A-	3767472	12-07-73
		CH-A-	572914	27-02-76
		CA-A-	1010041	10-05-77
		BE-A-	778269	19-07-72
		OA-A-	4087	30-10-79
		SE-B-	404604	16-10-78
DE-A- 3530793	27-03-86	EP-A-	0174464	19-03-86
		JP-A-	61072782	14-04-86
		US-A-	4704387	03-11-87

MP0289

4

Arzneimittel

Fortschritte 1972 bis 1985

Herausgegeben von
Axel Kleemann, Ernst Lindner und Jürgen Engel

Fortführung des von G. Ehrhart und H. Ruschig begründeten Werkes

Arzneimittel

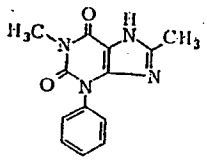
Entwicklung, Wirkung, Darstellung

VCH

ıny), 1987

NY 10010-4606

Tab. 12-5. (Fortsetzung.)

Nr.	Name (INN, Prüfbezeichnung)	Formel	Handelsname	Literatur
38	D 4026			[85(H)]

Hydrolyse Theophyllin frei, wodurch therapeutische Blutspiegel über einen Zeitraum von 12 Stunden erhalten werden [82]. Beim BB-1502 37 liegt mit einem cyclohexylsubstituierten Adeninderivat eine neuartige Verbindung vor. Mit den bisher beschriebenen Theophyllinderivaten hat es den Hauptwirkungsmechanismus, die Phosphodiesterasehemmung, gemeinsam [42, 84]. Gegenüber Theophyllin-Ethylendiamin (*Aminophyllin*) zeigt die Substanz längere und stärkere Wirkung bei gleichzeitiger besserer kardiovaskulärer Verträglichkeit. Im D 4026 38 ist eine Methylgruppe des Xanthingerüsts durch einen Phenylrest substituiert. Die Verbindung verhindert Antigen-induzierte Konstriktionen auch bei oraler Applikation [85]. Sie ist ferner imstande, die IgE-bedingte Freisetzung von Histamin in menschlichen Leukocyten zu verhindern [85].

12.3.2.4 Antiasthmatika-Antiallergika

Beim allergisch bedingten Asthma können sowohl Hemmstoffe der allergisch bedingten Mediator-Freisetzung („Release"-Inhibitoren, Typ des DNCG) als auch Inhibitoren der Mediator-Wirkung (Antagonisten) therapeutisch eingesetzt werden. DNCG (DSCG, **Cromoglycinsäure** Dinatriumsalz, *Intal*) ist in Deutschland seit 1972 im Handel. Die Nachfolgesubstanzen weisen sehr heterogene Strukturen auf. Auch die Wirkungsweise dieser Therapeutika läßt sich nicht ohne weiteres auf einen Nenner bringen. Die vorwiegend prophylaktische Wirksamkeit scheint auf mehreren Wirkungsmechanismen zu beruhen (u.a. antihistaminerg, anti-SRS-A, immunologisch). Die in Tabelle 12-6 aufgelisteten Wirkstoffe, wie z. B. **Ketotifen 39, Oxatomid 40, Azelastin 43, Lodoxamid 44, Nivimedon 45, Oxarbazol 46** und **Tranilast 42** sollen gegenüber DNCG den Vorteil der oralen Wirksamkeit aufweisen.

Ketotifen 39 ist eine Weiterentwicklung des Serotonin-Antagonisten **Pizotifen** (*Sandomigran*), das als Migränemittel eingesetzt wird. **Ketotifen 39**, ein stark wirksames H_1-Antihistaminikum mit zusätzlichen antianaphylaktischen, mastzellstabilisierenden Eigenschaften wird vorbeugend gegen Asthmaanfälle, Schnupfen und Hauterkrankungen auf allergischer Basis empfohlen [42, 85].

Oxatomid 40, chemisch ein Dimethylpiperazin-Derivat [86, 87] ist ebenfalls ein stark wirksames Antihistaminikum, das in vitro und in vivo antiallergisch-antianaphylaktisch wirkt. Es besitzt mastzellstabilisierende Eigenschaften und antagonisiert Histamin und

Tab. 12-6. Antialle

Nr.	Name (Prüfbez
39	Ketotife
40	Oxatom
41	Tiaram
42	Tranila: N'-5
43	Azelast A-5610
44	Lodoxa U-42,7
45	Nivime BRL-1

Azelastin 43 ist chemisch ein Phthalazinon-Derivat. Neben einer starken Antihistaminwirkung besitzt es ausgeprägte antiallergisch-antianaphylaktische Wirkung [14, 15, 42, 91, 92, 93]. Als Wirkungsmechanismus wird ein zweifacher Angriffspunkt — Hemmung der Mediatorfreisetzung über Mastzellstabilisierung und Antagonisierung von Mediatoren (Histamin, SRS-A, evtl. Serotonin) — angenommen. Eine Hemmung der Bildung bzw. Freisetzung von SRS-A und eine Antagonisierung des bereits freigesetzten SRS-A konnte experimentell belegt werden [94].

Nivimedon 45 verhindert die durch IgE hervorgerufene Hypersensibilität in Ratten. Eine ähnliche Wirkung wird am Menschen erwartet [96].

Lodoxamid 44 ist im Test der passiven cutanen Anaphylaxie der Ratte bei intravenöser Verabreichung im Vergleich zum Dinatriumsalz der **Cromoglycinsäure** um den Faktor 2500 wirksamer [95].

Zaprinast 47 ist ebenfalls in mehreren tierexperimentellen Untersuchungen wirkungsstärker als das Dinatriumsalz der **Cromoglycinsäure** [98]. Die Koplanarität des Phenylrings mit dem Azahypoxanthingerüst ist Voraussetzung für die hohe antiallergische Aktivität [99].

Aus bisher vorliegenden Tierexperimenten geht die stärkere Wirksamkeit von BL-5255 **48** im Vergleich zu dem Dinatriumsalz der **Cromoglycinsäure** und **Lodoxamid 44** hervor. BL-5255 **48** ist oral wirksam bei fehlenden Antihistamin-Eigenschaften [100].

WY-41195 **50** [102] entfaltet bei oraler Applikation eine starke Hemmwirkung gegenüber der durch IgE ausgelösten, passiven kutanen Anaphylaxie der Ratte und erwies sich ebenfalls als hochwirksam im Versuchsmodell der passiven Lungenanaphylaxie. Die Verbindung weist minimale Phosphodiesteraseaktivität auf und hat keine bronchialerweiternde oder antihistaminische Wirkung [103]. Klinische Daten liegen noch nicht vor.

12.3.3 Neuere Entwicklungen

In jüngster Vergangenheit sind auf dem Gebiet der Atemwegstherapeutika, speziell der Antiasthmatika, einige hochinteressante Entwicklungsansätze zur Verbesserung der Therapiemöglichkeiten publiziert worden. Neuere Befunde [124, 125] weisen auf die pathophysiologische Bedeutung der Leukotriene im allergischen und asthmatischen Geschehen hin (siehe ebenso Kapitel 11). Weiterhin ist die Funktion von PAF („platelet activating factor") als Mediator bei Asthma und Entzündungsprozessen Gegenstand intensiver Untersuchungen [126]. Ein Eingriff in die Lipoxygenase-Kaskade ist auf mehreren Wegen möglich:

1. Verminderung der Bereitstellung von Arachidonsäuresubstrat durch spezifische Inhibitoren der Phospholipase A_2 [127] und/oder der Peptidleukotrien-Glutathion-S-Transferase.
2. Hemmung der 5-Lipoxygenase [128].
3. Hemmung der Leukotrienfreisetzung.
4. Hemmung der Leukotrien-Effekte an den die Broncho- und Vasokonstriktion vermittelnden Rezeptoren durch Antagonisten.

Summarisch werden nach heutigem Kenntnisstand die folgenden Mediatoren mit der Symptomatologie beim Asthma in Verbindung gebracht [129]: Kontraktion der Bronchial-